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Small Intestinal Bacterial Overgrowth (SIBO): Diagnostic Challenges and Functional Solutions

The human gut microbiome is now recognized as having a major influence on a wide range of human physiological processes, many of which influence a person's risk for non-gastrointestinal diseases (e.g., cardiometabolic, neurodegenerative, immunological, etc.). Research findings have shown strong associations between the presence or absence of certain microbes (primarily bacteria in stool samples) and specific clinical conditions, spurring numerous debates over the best way to define the microbe communities within the human GI tract and whether there is an "ideal" human gut microbiota. While these debates continue, there is general agreement that any prolonged disturbance in the gut microbiome (i.e., dysbiosis) is harmful to the health of the host; and of the many conditions which fall under the definition of dysbiosis, small intestinal bacterial overgrowth (SIBO) has been of recent clinical and research interest.

SIBO was initially described in connection with malabsorption syndromes primarily related to anatomical dysfunction of the GI tract, such as in blind loop syndrome, or in cases of anatomical dysfunction following GI surgery (e.g., gastric bypass).[1] It was in this historical context that the name small intestinal bacterial ***overgrowth*** emerged, since there was a notable increase in culturable bacteria from small intestinal aspirate samples in these subjects. However, current molecular techniques now used for evaluating the gut microbiota suggest that simple enumeration of bacteria does not adequately capture the relationship between the clinical manifestations labeled as "SIBO" and the alterations in the microbiome of the small intestine. Furthermore, since breath-testing is more commonly used to define SIBO in most clinical and research settings, the interface between a clinician's practical understanding of SIBO and the published literature related to this topic is sometimes difficult to navigate.

Today, SIBO (by various definitions) has been associated with many systemic health conditions such as obesity,[2] nonalcoholic steatohepatitis,[3] systemic sclerosis,[4,5] type 2 diabetes,[6] as well as many GI-related conditions, such as irritable bowel syndrome (IBS), Crohn's disease,[7] and celiac disease.[8,9,10] For the clinician attempting to practice functional or integrative medicine, understanding the potential connection between small intestinal microbiome disturbances and these other conditions may aid in choosing a therapy that focuses on its root cause rather than its manifestation. In this monograph, we summarize the many ways SIBO is defined, showing how these definitions can greatly influence the clinical approach. In addition, by describing the underlying causes leading to small intestinal microbiome dysbiosis, we suggest that SIBO may be best viewed as a clinical consequence of other functional issues, rather than a diagnostic endpoint (i.e., a disease). A review of the most common therapies used to resolve SIBO is also included.

The Small Intestinal Microbial Ecosystem: What is Normal

During the 1960s and 1970s researchers began publishing data related to the microbial communities within the human GI tract (e.g., stomach, small intestine and colon) in both healthy subjects and those with various GI abnormalities.[11,12] From these simple investigations of culturable bacteria, researchers began to understand that although the GI tract is one continuous segment of tissue, it is a complex organ system with very distinct environmental niches throughout. The anatomy and function of each segment creates a series of unique local environmental conditions (e.g., pH, motility patterns, mucosal thickness, nutrient availability, oxygen gradient, etc.) which influence the types and quantities of microbes found in each area of the GI tract (see Figure 1). Among the many features defining the small intestinal microbiomes are the relatively low abundance of all culturable bacteria (10^2-10^5 CFU/mL), especially in the duodenum and jejunum, populated mostly with gram-positive, aerobic bacteria. In comparison, the microbial ecosystems of the colon (and distal ileum) are characterized by much higher numbers of bacteria, with a predominance of gram-negative, anaerobic organisms.

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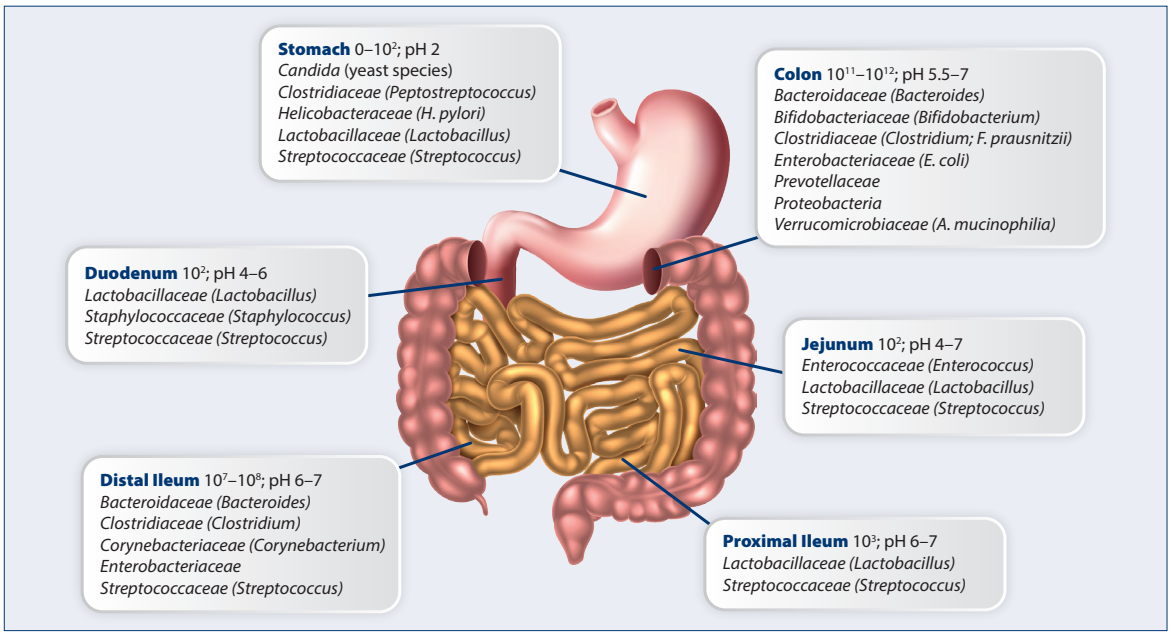

Figure 1. General Heterogeneity of GI Microbial Habitats. Microbial species are not uniformly distributed amongst the various niches and locations along the GI tract as illustrated by this figure and discussed in the text. Differences in nutrient availability, pH, mucosal viscosity, and a number of other factors contribute to the heterogeneity of the microbial species. Notice the lower relative abundance of microbes in the small intestine compared to the colon, and the differences in the types of microbes present in these two areas of the GI tract.

Small intestinal bacterial overgrowth (SIBO), a condition with non-specific clinical symptoms (e.g., bloating, abdominal distension/pain/discomfort, diarrhea, fatigue, weakness, etc.) was first described in subjects with anatomic abnormalities of the digestive tract, such as those with stagnant blind loop syndrome or abdominal surgery. The condition was defined as an "overgrowth" of bacteria in the small intestine since the method used to evaluate the microbial ecology of the small intestine relied solely upon the quantification of the culturable microbes present in an aspirate sample from the small intestine. For instance, jejunal aspirate culture counts have been shown to be higher in those with stagnant loop syndrome (>10^5 CFU/mL) compared to healthy controls (≤10^3 CFU/mL).[13] As research progressed, SIBO began to be studied in subjects without "a demonstrable anatomic abnormality," suggesting that other small intestinal microbial disturbances may also be associated with similar symptoms.[1] In fact, in a 1979 review article, Gracey suggested a more inclusive term for this phenomenon called, the "contaminated small bowel syndrome." [1]

Despite the traditional understanding of SIBO being merely an overgrowth phenomenon, recent research using molecular technologies has allowed researchers to question whether various "SIBO" symptoms are linked solely to the quantity of microbes in the small intestine, or whether they may be linked to specific types of microbes present in the small intestine or to the metabolic alteration of normal commensal organisms. For instance, some researchers have suggested the retrograde displacement of gram-negative microbes from the colon into the small intestine represents a different clinical entity than an increased abundance of gram-positive microbes typically associated with the upper GI tract.[14] Unfortunately, these emerging technologies have not yet been incorporated into the definition(s) or diagnostic criteria for SIBO, something we hope will be remedied in the near future. Therefore, while the current diagnostic criteria used to define SIBO (i.e., aspirate culturing and breath-testing) are generally lumped together in research and clinical settings, we believe these manifestations likely represent numerous different small intestinal microbial disturbances with a variety of functional root causes, only some of which include a numerical overgrowth of bacteria. For this reason, it is important for clinicians to understand the different ways that SIBO is currently defined and diagnosed.

Diagnosing (and Defining) SIBO

The clinical presentation of SIBO can differ in each patient, though it is usually associated with non-specific GI symptoms, such as bloating, flatulence, abdominal discomfort and distension, chronic diarrhea, steatorrhea, etc.[15] In severe cases, SIBO has been associated with diarrhea-induced weight loss or weight loss due to poor oral food consumption.[16] Further, SIBO is often characterized by nutrient deficiencies, especially malabsorption of fat (steatorrhea), vitamin B_{12}, iron, thiamin and nicotinamide (macrocytic anemia may occur due to vitamin B_{12} deficiency), and several fat-soluble vitamins (A, D, E).[16,17,18,19] Ironically, since bacteria synthesize folate, levels of folate have been notably increased in some subjects with SIBO.[20,21] In rare cases, patients with SIBO and short-bowel syndrome may present with D-lactic acidosis following a high carbohydrate meal, and symptoms may

include slurred speech, confusion, ataxia, seizures, etc.[16] Since many of these symptoms are non-specific and may be associated with a range of functional bowel disorders, it is difficult to diagnose SIBO based on symptoms alone. For this reason, the diagnosis of SIBO is usually based upon direct enumeration of small intestinal bacteria, or by surrogate measurement of their fermentation activity via breath testing (or by an empiric course of antibiotics).[22]

Small Intestinal Aspirate and Culture

Based upon the original definition of SIBO, enumeration of bacteria sampled from the small intestine seems straightforward. This is basically performed using a sample gathered from aspirating the small intestine (traditionally the jejunum), followed by culturing and enumerating the bacterial colonies in a laboratory. This method has often been regarded as the "gold-standard" for defining SIBO, though many have argued that this method is simply a legacy from tradition, using a primitive methodology that was never properly validated.[13,23] Obviously, this method is invasive, time-consuming, costly, and requires careful aseptic technique; and it can only measure those microbes that can be cultured in a laboratory. In addition, it is now evident that sampling from one location in the small intestine may not represent the various microbial niches in other areas of the small intestine.[24] Therefore, while aspiration and enumeration may be the foundation for the original definition of SIBO, there is much disagreement on how it should be used for diagnostic purposes.

In their systematic review of 71 publications regarding diagnostic tests for SIBO, Koshini et al. (2008) found much heterogeneity in terms of the location of aspirate samples (duodenum or jejunum) and the cut-off value used to define SIBO (22 studies used $>10^5$ CFU/mL, three used $>10^4$ CFU/mL, seven used $>10^6$ CFU/mL and one used $>10^7$ CFU/mL, while 14 others used variable definitions).[13] Further, their review of the literature suggests that the cut-off value for defining SIBO of $>10^5$ CFU/mL was more indicative of the microbial ecology of blind loop syndrome, while other GI disorders associated with increased levels of microbes may present at a lower threshold. Nonetheless, careful aspiration and enumeration are still used in many clinical trials (often compared to breath testing) to understand the association of SIBO with other conditions or treatments (e.g., PPI use, IBS, antibiotic therapies, probiotic use, etc.). The ACG guidelines for SIBO suggest that the use of $>10^5$ CFU/mL is too stringent a diagnostic cut-off for subjects without structural GI disorders and, therefore, recommend (with the North American Consensus) that a threshold of $>10^3$ CFU/mL should be used as a diagnostic criteria for SIBO.[22,25]

Breath Testing

The most common surrogate diagnostic test for SIBO indirectly measures the metabolic activity of microbes in the small intestine by measuring the breath of the host. Specifically, after ingesting a carbohydrate substrate which can be fermented by certain GI microbes (commonly lactulose or glucose), the amount and timing of gaseous by-products are measured from breath samples collected over several hours. The most commonly measured gas for SIBO breath testing is hydrogen, as it is exclusively produced by microbes; however, some labs also test for methane, as hydrogen can be consumed by certain microbes to produce methane, which may result in a false-negative result for "SIBO" (see sidebar for more details on methane production and testing). Hydrogen can also be used to produce hydrogen sulfide, and some labs have suggested hydrogen sulfide should also be analyzed in breath testing to exclude false negative results or identify the activities of certain species of bacteria.[26] Breath testing relies upon fermentation of the carbohydrate substrate in the small intestine (if certain bacteria are present), the production of metabolic byproducts (e.g., hydrogen, methane, hydrogen sulfide, etc.), the diffusion of these gases into the bloodstream, and eventually the expiration of these gases through the lungs and into the testing apparatus at specified time intervals.

Glucose is readily absorbed in the proximal small intestine, so the increase in breath hydrogen following glucose absorption signals inappropriate fermentation caused by rogue microbes in the small intestine that ferment glucose prior to its absorption. Lactulose, on the other hand, is a non-absorbable carbohydrate that escapes absorption in the small intestine and is readily fermented by bacteria in the colon. Elevated or early fermentation of lactulose implies the presence of colonic (or other) bacteria in the small intestine. In some cases, a double peak of hydrogen in the breath test following lactulose ingestion is considered a positive indication of small intestinal fermentation (the second peak is interpreted as the normal colonic fermentation of lactulose, suggesting the early peak occurred in the small intestine). Based on the time-course and magnitude of elevation of these microbial by-products, inferences are made about the microbes in the small intestine and their fermentation pattern. Consequently, it is important to remember that breath testing indirectly measures the activity of certain small intestinal microbes and is not directly measuring an "overgrowth." In addition, since the timing of the rise in breath hydrogen may be influenced by orocecal transit time in some subjects (especially when using lactulose), the relationship between "breath test positive" and "SIBO" is often imprecise.[27,28,29,30] These limitations have led to various disputes about the utility of breath testing in general, or the superiority of one substrate over another; issues which are explored further below.

"Breath Test Positive": A Surrogate Diagnosis

Even after the publishing of the North American Consensus on this subject in 2017, there is still disagreement on the optimal substrate(s) and methods for using breath testing as a surrogate diagnosis for SIBO.[25] Years ago, in the systematic review of diagnostic tests for SIBO described previously, Khoshini et al. (2008) note that much heterogeneity existed in the literature concerning the methods used to define SIBO via breath-testing,

such as characteristics of the gas peak, the frequency of measuring breath samples, and the thresholds used to define a positive test. Further, the meta-analysis suggests that because glucose is absorbed readily in the proximal small intestine, the use of glucose as a substrate appears to be a better measure for proximal bacterial overgrowth/activity, whereas the use of lactulose in those with rapid transit may result in a false positive diagnosis. A decade later, these same issues remain a concern for many researchers.[31,32,33]

Methane Breath Test

The North American Consensus report for the use of breath testing in gastrointestinal disorders such as SIBO recommends adding methane testing when using the lactulose or glucose breath tests.[25] Methane testing is recommended since many methanogenic Archaea in the gut use hydrogen to form methane (four molecules of hydrogen are used by methane-producing Archaea to produce one molecule of methane). Therefore, excess activity of methanogenic organisms will consume a significant amount of the bacterial-produced hydrogen, which may result in a false-negative hydrogen breath test.[40] In fact, one group of researchers evaluated a large-scale lactulose breath test database and found that of 14,043 breath tests, 17.2% were positive for methane, while also being significantly lower in breath hydrogen values ($P < 0.0001$).[41] From a diagnostic stand-point, significantly fewer hydrogen breath tests indicative of SIBO (i.e., ≥20 ppm rise of hydrogen) were found in methane producers (23.1%) compared to non-methane producers (55.7%; OR: 0.20, 95% CI: 0.18 – 0.22), suggesting that methane production "dramatically alters the interpretation of hydrogen in breath testing for identification of bacterial overgrowth." [41]

Not only does the presence of methane potentially affect the results of the breath test, but methane production has been strongly linked with constipation. One systematic review and meta-analysis suggests methane is significantly associated with constipation with an OR of 3.51 in the study population of 1,277 subjects (95% CI: 1.84-6.56).[42] Because of the potential for interference with the hydrogen breath test, and because methane production may be associated with a clinically meaningful presentation (i.e., constipation), we recommend methane testing whenever hydrogen breath testing is performed. For methane, a concentration ≥10 ppm in any of the breath samples is considered positive for methanogenic activity.

Interestingly, while many use the term "methane-positive SIBO" or similar terms when a patient has a positive methane breath test, the newer term "intestinal methanogen overgrowth" (IMO) is currently being suggested as the more appropriate nomenclature. This is because methane is produced by Archaea (rather than true bacteria) and results from fermentation in both the large and small intestines.[22,43,44]

As noted previously, one of the current assumptions and limitations of breath testing as a diagnostic indicator for SIBO is not accounting for differences in intestinal transit time.[34] Since the average transit time is shorter in some populations, this is considered the main cause of frequent misinterpretation of an early hydrogen peak after lactulose ingestion.[29,35,36,37] This is an important limitation since the breath test is interpreted as measuring ***small intestinal*** bacterial fermentation, which can be confounded by early colonic fermentation caused by fast transit time. In fact, research groups have shown that the performance of both the lactulose (LBT) and glucose breath tests (GBT) are influenced by orocecal transit time.[25,27,29,30,38] These studies measure orocecal transit time (commonly using scintigraphy) concurrently with hydrogen breath tests to evaluate whether the rise in breath hydrogen occurs before or after the test substrate reaches the cecum. For instance, one study combined the lactulose breath test with ^{99m}Tc scintigraphy in a group of IBS subjects and found that the ^{99m}Tc reached the cecum in 88% of patients before the abnormal rise in breath hydrogen occurred.[29] In another study (N = 139), 65% of patients who had undergone upper GI surgery and 13% of subjects who had not undergone surgery were deemed to have a false-positive glucose breath test related to transit time.[27] In yet another study, glucose malabsorption in patients with chronic diarrhea resulted in rapid orocecal transit time (measured by nuclear transit), which led to "positive" glucose breath test results; the authors suggest that combining glucose breath testing with a nuclear transit scan may improve the accuracy of hydrogen breath tests in the diagnosis of inappropriate bacterial-dependent fermentation within the small intestine.[39]

Precautions related to transit time have even been confirmed using the newest technology for measuring intestinal gas formation, a telemetric capsule which transmits data to an external receiver as it passes through the GI tract. This technology found that 40 g doses of glucose can lead to increases in hydrogen gas in the colon due to malabsorption, which is in agreement with the studies comparing glucose breath tests with scintigraphy using much higher doses of glucose (usually around 75 g).[34] This capsule also enabled the quantification of transit times through the small intestine by comparing oxygen concentrations to hydrogen levels – this allows the estimation of the anatomical location of the capsule, which may be critical to the interpretation and significance of hydrogen concentrations. Although more research needs to be done to validate the ability of this gas-sensing capsule to measure anatomical location and the timing of fermentation (depending on the substrate used and whether the substrate travels faster or slower through the GI tract than the capsule), this appears to be an interesting new development for studying fermentation within the GI tract and may be a potential tool for redefining and diagnosing SIBO in the future.

Even with all these challenges and nuances, the American College of Gastroenterology generally agrees with the North American Consensus that a positive hydrogen breath test, defined as a hydrogen increase of ≥20 ppm from baseline

within 90 minutes of ingesting glucose (75 g) or lactulose (10 g), is diagnostic for SIBO. According to this guideline, a double peak for lactulose is not necessary for a SIBO diagnosis if the rise in hydrogen occurs prior to 90 minutes.

Comparing Breath Testing with Aspirate Enumeration

Since both common diagnostic methods have their limitations, several studies have investigated how these methods would diagnose SIBO, comparatively, in the same subjects. Ghoshal et al. performed a comparison of each breath test (glucose and lactulose) using various interpretations (i.e., single peak, double peak; hydrogen and/or methane) with the "gold standard" microbial quantification of upper gut aspirates in 80 subjects diagnosed previously with irritable bowel syndrome.[45] In this cohort of IBS subjects, 15 subjects had SIBO as defined by an upper gut aspirate above 10^5 CFU/mL (though 18 additional subjects had levels between 10^3 to 10^5 CFU/mL, considered to meet the threshold of SIBO by the ACG guideline standards). Compared to aspirate enumeration (deemed by the study design to be 100% sensitive and 100% specific), each of the breath tests were analyzed for their relative sensitivity (ability to correctly identify SIBO when present) and specificity (ability to accurately identify a SIBO-negative subject). They found that using the glucose hydrogen breath test, only four of the 15 SIBO subjects had a positive breath test (27% sensitive), while none of the SIBO-negative subjects had a positive breath test (100% specific). The lactulose breath test included two diagnostic categories: (1) an early hydrogen peak, which detected one more SIBO patient than the GBT (5/15 or 33% sensitivity) but incorrectly labeled 23/65 non-SIBO subjects with a "false" positive breath test (35% sensitivity); and (2) a double-peak interpretation, which was positive for only one (non-SIBO) subject (0% sensitivity, 98% specific). Using methane measures only in the lactulose group also had limited sensitivity (13.3%) and specificity (41.3%). Emerging research using molecular techniques and new methods for sampling and extracting bacterial DNA from small intestinal aspirate samples suggests better correlation may be found using these techniques in comparison to the lactulose breath test, especially at the 90-minute timepoint.[46]

These results clearly illustrate what many have suggested: breath tests are prone to misinterpretation or over-interpretation, at least in terms of defining "breath test positive" as a bacterial *overgrowth* in the small intestine when compared to small intestinal aspirate and culture.[23,36,47] In one study performed in India, comparing the LBT and the GBT in 175 IBS-D and 150 apparently healthy controls, the LBT was unable to differentiate between these two groups (34.3% and 30% positive breath test, respectively), while the GBT showed a statistical difference between these groups (6.2% and 0.66% positive breath test, respectively).[48] These differences also highlight the wide variability of the association between SIBO and IBS reported in the literature (see IBS and SIBO on page 11).

A Rome Consensus Conference, published several years prior to the data described above, suggested the sensitivity and specificity of the lactulose breath test were 52.4% and 85.7%, respectively; and glucose breath tests were 62.5% and 81.8%, respectively.[49] Overall, the Rome Consensus statements related to SIBO are: (1) The jejunal aspirate culture is traditionally considered the gold standard diagnostic test for SIBO, despite some serious methodological limitations and lack of accessibility to clinical practice; and (2) Glucose breath test is the most accurate hydrogen breath test for non-invasive diagnosis of SIBO. The addition of methane to hydrogen is helpful in capturing the overgrowth of methanogenic organisms common in about one in five subjects (i.e., improving sensitivity), though this may not increase the poor specificity of these tests.[50] Elevated methane-producing organisms increase the likelihood of constipation fivefold.[42] However, The Rome group does not recommend routine testing for SIBO.[15]

In contrast to the Rome Consensus, the North American Consensus group† on hydrogen and methane-based breath testing published their recommendation for breath testing in 2017.[25] The North American group contends that there is no reliable gold standard to compare breath testing, arguing that the use of the 10^5 CFU/mL as the enumeration definition of SIBO is a carryover from extreme cases (such as those with blind loop syndrome) – the group suggests that a threshold value of $>10^3$ CFU/mL may be a better upper limit for defining SIBO when using aspirate and culture. This group also contends, "glucose and lactulose breath tests remain the least invasive alternative to diagnose SIBO." Due to the large amount of heterogeneity in the literature surrounding the methods used and interpretation of breath testing, the North American Consensus group suggested a few parameters for breath testing: the ingestion of 10 g lactulose or 75 g glucose as substrates for breath testing, and that a rise in hydrogen by ≥20 ppm within 90 minutes during either breath test is suggestive of SIBO. The group also emphasizes the importance of measuring methane along with hydrogen (see sidebar), but they additionally emphasize measuring carbon dioxide (or oxygen) to adjust the breath sample for non-alveolar dilution of exhaled air. The North American Consensus group suggest methane levels ≥10 ppm are considered indicative of a positive methane sample. The consensus group encourages future research to integrate deep sequencing techniques to further assess the bacterial diversity in SIBO subjects.

Breath Testing, Our Recommendation

Based upon the comparison of breath testing with aspirate enumeration, we suggest that there should be a distinction between "breath test positive" and "SIBO." A positive breath test is merely the evidence of elevated or early production of gas from the bacterial fermentation of undigested carbohydrates. Several

† Consists of 17 clinician-scientists from high-volume breath-testing referral centers in various parts of the US, Mexico, and Canada who are actively publishing breath testing research. We should note that financial support for the consensus group was provided, in part, by Commonwealth Laboratories, a company offering breath tests for SIBO outcomes.

functional issues can create a positive breath test (e.g., rapid transit time, carbohydrate maldigestion/malabsorption, poor sampling technique, etc.) concomitant with or independent of a small intestinal bacterial overgrowth. Clinicians should consider using breath testing to screen for specific dysbiotic conditions that lead to fermentation, especially when the test results are likely to alter the therapeutic decision-making strategy. Clinicians should check with existing labs for their available test methods, substrates, and cut-offs points. A note of caution: since breath testing is highly dependent on proper test methods, including stringent pretesting dietary restrictions, clinicians should be careful to ensure that the patient understands these restrictions and can perform the test, at home, as instructed (see Box below); and that adherence to these instructions are confirmed before a positive diagnosis is given.

Preparation for the Breath Test

Adequate preparation for breath testing is essential for proper interpretation, as many factors can affect the results. Therefore, it is vital that patients are made aware of the extensive preparation that is required and admonished to read the test kit instructions thoroughly. Factors such as eating a complex carbohydrate meal prior to testing, exercising, or cigarette smoking during the test, not rinsing with an antiseptic mouth rinse, etc. can affect the subject's baseline hydrogen levels and may impact levels during the test. Here is a list of the breath test preparation recommendations taken from the 2017 North American Consensus statement on hydrogen and methane-based breath testing in gastrointestinal disorders:[25]

- *We recommend that antibiotics should be avoided for 4 weeks prior to the breath test.*
- *A firm position statement cannot be reached due to lack of conclusive data on stopping or continuing pro/prebiotics prior to breath testing.*
- *We suggest that, if tolerated by the patient, promotility drugs and laxatives should be stopped at least 1 week prior to breath testing.*
- *We suggest that fermentable foods such as complex carbohydrates should be avoided on the day prior to breath testing.*
- *We suggest that the fasting period for breath testing as part of preparation should be 8–12 h.*
- *We recommend that smoking should be avoided on the day of breath testing.*
- *We recommend that physical activity should be limited during breath testing.*
- *We suggest that it is not necessary to stop proton pump inhibitors prior to breath testing.*

Molecular Analysis of SIBO Microbiome

Molecular techniques have already shown that distinct regions of the small intestine have distinct microbial compositions compared to other areas of the GI tract and the stool.[51,52,53,54] In fact in 2008, Khoshini et al. suggested that molecular techniques based on genomic and metabolomic methods may prove to be the most precise methodology for the diagnosis and definition of SIBO, especially as there is increasing interest in defining which bacteria are present, rather than just the quantity of bacteria in the small intestine.[13] However, until recently, very few research groups were using these techniques to evaluate the small intestinal microbiota in SIBO patients, as there was not a standardized method developed to sample, process, and sequence samples from the small intestine.[53] Currently, the preponderance of research on the gut microbiota has been done on stool samples; however researchers have learned that the techniques used to sample and process stool samples cannot be directly applied to samples from the small intestine due to the location of sampling and the physical properties of the small intestinal contents (i.e., high viscosity due to mucus content).

The REIMAGINE (Revealing the Entire Intestinal Microbiota and its Associations with the Genetic, Immunologic, and Neuroendocrine Ecosystem) study was designed to specifically address this gap in the research.[46,55] This study developed and validated methods to optimize sample collection and sample processing from the small intestine. Some novel techniques developed in this study include a custom-designed catheter that samples the duodenum but avoids contamination from the proximal GI tract and sample preparation using dithiothreitol (DTT) to cleave disulfide bonds in mucus to improve DNA recovery. Through this work, the REIMAGINE study group has found that the microbiota of the small intestine is markedly different than the stool microbiome and also varies between small intestinal segments (i.e., duodenum, jejunum, and the furthest distance reached).[24] In fact, using 16S rRNA sequencing, the REIMAGINE study identified differences in more than 2,000 operational taxonomic units between the small intestinal and stool microbiomes.

The REIMAGINE study used its methods to compare the small intestinal microbiota composition of healthy subjects to those with SIBO using data from patients undergoing upper gastrointestinal endoscopy without colonoscopy.[46] In this study, SIBO was defined as $>10^3$ CFU/mL bacteria on MacConkey agar plates. Of the 140 subjects tested, 98 subjects had bacterial counts less than the threshold for SIBO ($<10^3$ CFU/mL) and were defined as non-SIBO; while 42 subjects had bacterial counts $>10^3$ CFU/mL and were classified as SIBO subjects. Subjects with SIBO had 4×10^3 fold higher bacterial counts than non-SIBO subjects on MacConkey agar plates ($P < 0.0001$). Major differences were also found in the microbiota composition when comparing 16S rRNA duodenal samples from SIBO subjects to non-SIBO subjects. First, SIBO subjects had significantly lower alpha-diversity than non-SIBO subjects. Secondly, major differences were seen at the phyla

level. The dominant phyla in non-SIBO subjects was Firmicutes; however, the dominant phyla in SIBO subjects was Proteobacteria which was 3.19-fold higher than non-SIBO subjects. The increased relative abundance of Proteobacteria in SIBO subjects was associated with a decreased relative abundance of Firmicutes.

Not only was the dominant phyla significantly altered in SIBO subjects compared to non-SIBO subjects, but the taxonomic composition of the dominant phyla, Proteobacteria, was also significantly altered. More specifically, within the Proteobacteria phyla there was an increased relative abundance of Gammaproteobacteria and a reduction in the class Alphaproteobacteria in SIBO subjects. *Klebsiella* species and other representatives of the family Enterobacteriaceae were also increased in subjects with SIBO as were species from the genus *Aeromonas* (family Aeromonadaceae). In addition to the gut microbiota compositional changes, this study evaluated microbial metabolic pathways and found that when compared to breath test outcomes, it appears that downstream metabolic pathways are altered in SIBO, suggesting that the microbiome of SIBO may have upregulated pathways that lead to H_2 production. In fact, the relative abundance of the class Gammaproteobacteria showed a positive correlation with increased production of H_2 at 90 minutes after lactulose intake; however, the relative abundance of the phylum Firmicutes showed a negative correlation with H_2 production at 90 minutes. The REIMAGINE study's results and the methods developed to sample and process specimens from the duodenum are pioneering and show the potential of molecular techniques to improve our understanding of the microbiota of the small intestine in a variety of dysbiotic states.

Although the results from the REIMAGINE study appear promising, research from other groups suggest that this area of research is still in its infancy and there is much to learn about the small intestinal microbiota in both healthy subjects and those with GI disorders. As such, not all groups attempting to compare the duodenal microbiota composition in subjects with gastrointestinal disorders have observed similar correlations between SIBO and small intestinal dysbiosis, perhaps owing to the fact that they use different methods than those used in the REIMAGINE study. In fact, using a retrospective chart review to obtain clinical metadata, Saffouri et al. compared duodenal aspirate samples from subjects with symptoms associated with functional GI disorders (FGIDs, N = 126) to healthy controls (N = 38) and found that GI symptoms were not associated with SIBO (defined as $>10^5$ CFU/mL) but, instead, were associated with small intestinal microbial dysbiosis via 16s rRNA sequencing.[56] Further, this study found SIBO (defined as $>10^5$ CFU/mL in duodenal samples) was associated with a high fiber diet even in healthy subjects without symptoms. These data show that while the application of molecular methods to study SIBO is an exciting new area of research, there is still much more to learn before definitive conclusions can be reached. These data also highlight the need for standardization of methods across studies so that results from different groups may be compared.

Etiology of Chronic Small Intestinal Dysbiosis

There are many physiological factors and innate defenses designed to help maintain a healthy balance between the host and their gut microbiota; failure in one or more of these systems can lead to a disturbance of the gut microbial environment (i.e., dysbiosis). Within the small intestine, these innate physiological defenses include: gut anatomy, gastric acid, bile acids, pancreatic enzymes, intestinal motility and transit time (including the migrating motor complex), and an intact ileocecal valve that prevents the retrograde translocation of bacteria from the colon to the small intestine. Using either aspirate enumeration or breath testing, investigators have associated failures in most of these defense systems with an increased prevalence of SIBO. These include hypochlorhydria, chronic pancreatitis, pancreatic exocrine insufficiency, anatomical abnormalities (e.g., small intestinal obstruction, diverticula, fistulae, surgical blind loop, previous ileocecal resection, etc.) and/or motility disorders (e.g., scleroderma, autonomic neuropathy in diabetes mellitus, post-radiation enteropathy, small intestinal pseudo-obstruction, etc.).[57] Here we discuss several of the strongest functional associations predisposing an individual to chronic small intestinal dysbiosis, including a formal diagnosis of SIBO.

Migrating Motor Complex and Intestinal Motility

Maintenance of small intestinal motility is often cited as the most important mechanism preventing unwanted microbial colonization in the small intestine. The normal motility pattern of the GI tract is governed by the migrating motor complex (MMC), which is a cyclical "housekeeping" motility pattern within the stomach and small intestine that, during fasting, functions to clear food or nonfood residue (e.g., secretions, microbes, debris, etc.) from the upper gastrointestinal tract.[58] Three distinct phases mark the MMC, of which the third phase is the most active, sweeping the luminal content from either the stomach into the duodenum or from the distal small intestine (ileum) into the colon. Phase III is also associated with a secretory phase, which triggers increased acid and pepsin secretion in the stomach and pancreatic secretion (i.e., water, bicarbonate, and enzymes) in the duodenum.[59]

The MMC follows a circadian rhythm (less active during sleep) and is regulated by a complex neurohormonal control mechanism by gastrointestinal hormones, the enteric nervous system, and the autonomic nervous system via the vagus nerve, although the specific mechanisms are not well understood.[60,61] Hormones that may be involved in MMC regulation include motilin, ghrelin, somatostatin, pancreatic polypeptide, serotonin (5-hydroxytryptamine, 5-HT), and xenin.[61] Considerable inter-individual variability marks the MMC (e.g., 113 to 230 minutes in one study), and the cycle is known to vary within the same individual as well (e.g., 58 to 70 minutes in one study).[62] Animal

and human studies have shown that a dysfunction or absence of Phase III of the MMC is associated with bacterial overgrowth of the small intestine.[63,64,65,66] In a 2002 case-control study which retrospectively enrolled IBS subjects with a previous positive lactulose breath test, Pimentel et al. found a reduced frequency ($P < 0.000001$) and duration of Phase III ($P < 0.001$) in IBS subjects who continued to have a positive lactulose breath test compared to the healthy controls. In a subgroup of the originally enrolled IBS subjects with positive LBT, subjects who were subsequently deemed to have had their "SIBO eradicated" (i.e., breath test negative, method of eradication not specified) had improved motility compared to those with SIBO persistence via positive LBT ($P < 0.05$).[67]

Many secondary factors contribute to disturbances in the motility pattern of the gut, including systemic diseases such as primary systemic sclerosis, Parkinson's disease, hypothyroidism, and diabetes mellitus (i.e., diabetic autonomic neuropathy); or the motility disturbances may result from radiation treatments or medications (e.g., opioids, anticholinergics, etc.). Narcotic use (evaluated through medical records) has been significantly associated with SIBO as measured via duodenal aspirate culture ($P < 0.05$); therefore, clinicians should consider this aspect of a patient's history carefully.[68,69] Additional factors contributing to changes in bowel transit time include extensive surgical resection (resulting in short bowel syndrome), creation of blind loops (e.g., Roux-en-Y bypass surgery, Billroth II procedure, etc.), anatomic risk factors (e.g., jejunal diverticulosis, stricture from Crohn's disease, or surgical anastomoses from small bowel resections), or intestinal pseudo-obstruction.[70] Interestingly, increased HPA axis stress has been shown to impair GI motility, through its inhibition of gastric emptying and stimulation of colonic motor function mediated by corticotropin-releasing factor receptor subtypes.[71] Though clinical trials attempting to modulate the stress response with SIBO-specific outcomes have not yet been published, the established gut-brain relationship mediated by the gut microbiota suggests that clinicians should be mindful of the role HPA axis stressors may play in a patient with SIBO.[72]

Prokinetic agents that affect the MMC and/or motility of the gut, have been suggested as potential therapeutics for SIBO outcomes; however, despite the biological plausibility of these agents reducing the risk for SIBO, published research evaluating these agents for their potential efficacy in this regard is still quite limited. We briefly review the commonly used pharmaceutical and natural prokinetic agents below.

Pharmaceutical Prokinetics

Low-dose Erythromycin

Although erythromycin is primarily used as a bacteriostatic macrolide antibiotic, at low doses erythromycin demonstrates kinetic effects on fasting motility.[73] In this respect, erythromycin functions as a motilin agonist. In a retrospective chart review, Pimentel et al. (2009) found preventative treatment with erythromycin (50 mg, at bedtime) after successful antibiotic treatment in patients with IBS and SIBO was associated with longer time to relapse (138.5 symptom-free days, N = 42) compared to subjects receiving no prevention (59.7 symptom-free days, $P = 0.08$, N = 6).[74] However, the use of a 5-HT4 receptor agonist was associated with more symptom-free days (see below).

5-HT4 Receptor Agonist

Serotonin plays a major role in the normal motility and secretory function of the gut and is produced by enterochromaffin cells in the mucosa of the gut. Once released in response to chemical and mechanical stimulation, serotonin increases intestinal peristalsis through the serotonin type 4 receptors (5-HT4). 5-HT4 receptors are also found in the central nervous system, urinary bladder, and atria of the heart. Serotonin type 4 receptor agonists are prokinetic agents that act on the serotonin receptors in the enteric nervous system to promote intestinal peristalsis, increase gastric emptying and decrease esophageal reflux.[75]

Representative drugs from this class include cisapride, tegaserod, and prucalopride. Cisapride was approved in the United States but was subsequently withdrawn after reports of life-threatening arrhythmias. Tegaserod was also once removed from the United States market because of an increased risk for cardiovascular side effects but was reintroduced for use in IBS-C in women under 65 years. Prucalopride is highly selective for the 5-HT4 receptor and is a potent stimulator of gastric motility.[76] Prucalopride differs from cisapride and tegaserod in having minimal activity against other serotonin receptors. Prucalopride has also been associated with minimal adverse side effects. Cardiac arrhythmias and prolongation of the QTc interval were not increased in those using Prucalopride. Prucalopride was approved as a therapy for chronic idiopathic constipation in 2018 and is now generally available.

As mentioned above, Pimentel et al. (2009) found preventative treatment with erythromycin (50 mg, at bedtime) after successful antibiotic treatment in patients with IBS and SIBO was associated with longer time to relapse.[74] However, preventative treatment with low-dose nocturnal tegaserod resulted in longer time to relapse (241.6 symptom-free days, N = 16) compared to no preventative treatment ($P = 0.003$) and to erythromycin ($P = 0.004$). Remission was four times longer with tegaserod compared to no therapy and nearly twice as long as erythromycin.

Natural Products with Prokinetic Effects

Ginger

Although ginger is perhaps best known for its anti-nausea effects, there is accumulating data suggesting ginger acts as a gastrointestinal motility stimulant.[77] Ginger has been found to increase gastric emptying in healthy subjects and those with functional dyspepsia when given as a challenge one hour before a low-nutrient liquid soup meal (500 mL). More specifically, fasted subjects with functional dyspepsia (N = 11) were given either 1200 mg of ginger root powder or placebo two hours before a low-nutrient soup meal; after the initial test, subjects crossed over to the other group after a seven-day washout period where they were

randomized in a double-blind fashion.[78] Compared to placebo, gastric emptying measured via ultrasound was more rapid after ginger ($P \leq 0.05$) and there was also a trend for more antral contractions after ginger ($P = 0.06$). Ginger supplementation in this context had no impact on GI symptoms nor on plasma concentrations of motilin, ghrelin or GLP-1. A similar study was done in healthy fasted subjects (N = 24) where ginger (1,200 mg) or placebo were given one hour before a low-nutrient soup meal (500 mL). In this setting ginger not only significantly improved gastric emptying compared to placebo ($P < 0.01$) but also significantly increased antral contractions ($P < 0.005$) and antral area ($P < 0.001$) compared to placebo when measured via ultrasound.[79]

Preclinical studies suggest the active components in ginger; namely, [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol, may affect gastrointestinal motility through interaction with serotonergic receptors.[80,81,82] Currently, the data suggesting this mechanism appear stronger for ginger's interaction with the 5-HT3 receptor related to its role in alleviating nausea; more research is needed to understand specifically how ginger or its components act at the level of the serotonergic receptors.

Interestingly, a small, randomized, cross-over pilot trial in healthy subjects (N = 11) evaluated the combination of ginger root extract (20 mg) and artichoke leaf extract (100 mg) for gastric emptying outcomes.[83] In contrast to giving ginger an hour before a test meal like the aforementioned studies, this study provided subjects with the active or placebo treatment ten minutes prior to a larger meal (i.e., 100 g tomato pasta, 100 g grilled meat, 20 mg chicory with oil and salt, and 300 g orange juice). When comparing ultrasound data before and after the meal, the researchers reported that the mean gastric area at baseline was 3.2 cm^2 while it was 8.4 cm^2 after the ginger/artichoke intervention and 11.0 cm^2 after the placebo. Therefore, the after-meal gastric area was significantly smaller following ginger/artichoke treatment compared to placebo (a -24% difference, $P < 0.001$). Further reductions in gastric area were seen when three subjects doubled the dose of the ginger/artichoke combination; however, the number of subjects evaluated was too low to evaluate statistically. Although the potential effect of ginger on gastric emptying appears promising (and is a common anecdote among clinicians treating SIBO), additional studies are needed to confirm that ginger's prokinetic potential improves patient outcomes in the context of SIBO to allow for specific dosing recommendations.

Iberogast

STW 5 (Iberogast) is an herbal preparation, originally manufactured in Germany, that dates to the 1960s and has been used for a variety of GI-related outcomes. Iberogast is composed of nine different herbal extracts including, bitter candy tuft (*Iberis amara*), fresh plant extract and extracts of lemon balm leaf (*Melissa officinalis*), chamomile flower (*Matricaria chamomilla*), caraway fruit (*Carum carvi*), peppermint leaf (*Mentha x piperita*), liquorice root (*Glycyrrhiza glabra*), Angelica root (*Angelica archangelica*), milk thistle fruit (*Silybum marianum*) and greater celandine herb (*Chelidonium majus*).[84] Iberogast has been shown to affect gastric motility in preclinical models. One study found application of Iberogast to muscle strips from all regions of the guinea pig stomach had regional-specific effects on gastric motility.[85] More specifically, Iberogast showed relaxation of the fundus and the corpus regions of the stomach, while Iberogast induced increases in the contractile force of the antrum. In the antrum, Iberogast augmented contraction amplitudes of the ongoing phasic activity without significantly affecting contraction frequencies. Similarly, Iberogast was suggested to have regional-specific action in the gastrointestinal tract when compared in a double-blind fashion to an ethanol-containing control solution in healthy male subjects in a series of small-scale experimental trials.[86] More specifically, compared to control, Iberogast increased proximal gastric volume ($P < 0.05$), increased the motility index of the antral pressure waves ($P < 0.05$), and slightly slowed gastric emptying of the liquid meal in the total stomach ($P < 0.01$); however, Iberogast had no effect on gastric emptying of solids, intragastric meal distribution, or on fasting duodenal or pyloric motility.

Hypothyroidism, Transit time and SIBO

Hypothyroidism has been associated with reduced gastrointestinal transit in animal and human studies and is therefore potentially linked to SIBO.[90-94] Hypothyroidism has also been associated with hypogastrinemia, a condition linked to slowing of bowel transit and reduced gastric HCl production.[95] Indeed, one study found a SIBO prevalence of 54% (measured via GBT) in subjects with overt hypothyroidism due to autoimmune thyroiditis (N = 50, TSH >2.8 µUI/mL, and decreased free T3 and free T4) compared to a prevalence of 5% in a group of control subjects (N = 40, $P < 0.001$).[96] The odds ratio for SIBO in the hypothyroid group was 22.3 (95% CI: 4.8-102.7). It should be noted that all hypothyroid subjects in this trial were supplemented with synthetic T4 hormone and achieved a euthyroid state 2-6 months prior to enrollment.

Interestingly, a large retrospective cohort study of 1,809 patients who had undergone hydrogen breath testing (LBT and/or GBT) found hypothyroidism (OR: 2.6) and especially levothyroxine therapy (OR: 3.0, 17.1% vs. 6.5%) had the strongest association with a positive breath test in their cohort (even compared to other factors like gastrointestinal surgery, motility, and the acid barrier).[97] Multivariate analysis found levothyroxine therapy was a stronger predictor of SIBO than hypothyroidism itself, though the specific mechanism is still not understood. Clinicians should be aware of this relationship, though more data are needed to determine a suitable therapy that improves both thyroid and small intestinal microbiome function.

Another study compared Iberogast to the 5-HT4 receptor agonist prokinetic cisapride in a head-to-head study in subjects with dysmotility type functional dyspepsia (N = 137).[87]

Although GI motility was not measured objectively, Iberogast (20 drops/day) and cisapride (10 mg/day) over four weeks were shown to have similar efficacy in the primary study outcome – the change in gastrointestinal symptom score. The average improvement in gastrointestinal symptom score was 84% of baseline value in the Iberogast treatment group comparable to 75% in the cisapride group. These results suggest non-inferiority of Iberogast compared to cisapride when evaluating improvement in GI symptoms. Although mechanism data suggest Iberogast may have a prokinetic effect and human data suggests that it may improve GI symptoms in subjects with functional dyspepsia and other functional GI disorders, additional research is needed to understand whether Iberogast has an effect on SIBO-related outcomes, as most clinical studies have evaluated symptom relief in subjects with functional gastrointestinal disorders.[88,89]

Hypochlorhydria and PPI Use

Low stomach acid (i.e., hypochlorhydria or achlorhydria) allows for increased survival of bacteria in the stomach and can compromise the regulation of microbial populations in the small intestine.[98,99] Conditions associated with compromised gastric acid production (e.g., atrophic gastritis, hypochlorhydria, gastric bypass, gastrectomy, proton pump inhibitor use, etc.) have been linked to a higher prevalence of SIBO.[98,100] In a cohort of elderly subjects with fasting hypochlorhydria (pH >3, as measured via gastric intubation and aspiration), the abundance of predominantly gram-positive microbes in the upper GI tract was greater than normal controls.[101] Twelve of the 15 elderly subjects had hypochlorhydria, with an average gastric pH of 6.6 and a mean bacterial count of 10^8 CFU/mL in the fasting gastric aspirate, while control subjects with normal stomach pH had fasting gastric aspirate samples $\leq 10^1$ CFU/mL. Interestingly, in this study, the microbiota in those with SIBO was dominated by gram positive microbes (e.g., Viridans streptococci, coagulase negative staphylococci, and *Haemophilus* spp.), with only one subject having significant concentrations of gram-negative bacteria (i.e., *Escherichia coli* [10^{4-5} CFU/mL] and *Klebsiella* [10^{4-5} CFU/mL]) – strict anaerobes were not found in these samples. Overall, this study suggests asymptomatic subjects with fasting hypochlorhydria may present with an overgrowth of predominantly gram-positive microbes, but the clinical significance of elevated concentrations of gram-positive organisms in the small intestine is not well understood.

The widespread use (or overuse) of proton-pump inhibitors (PPIs) as a contributing risk factor for SIBO is of concern to many.[98,99] A recent systematic review and meta-analysis found PPI users had a seven-fold higher incidence of SIBO (when defined by duodenal or jejunal aspirate overgrowth).[102] However, when SIBO was defined by a positive breath test in PPI users, the risk association was lower (OR: 1.93) and did not reach statistical significance. Interestingly, one study found an association between long-term PPI use and SIBO (by glucose breath test) in a cohort of subjects with gastric (N = 112) and colorectal cancer (N = 88).[147] Amongst the 116 subjects that were long-term PPI users, 74.1% tested positive for SIBO. In another study, long-term PPI use (>12 months) was associated with significantly higher amounts of total bacteria in gastric juice samples compared to short-term PPI users (3 months to 12 months); similarly, when sampling via duodenal brushing, long-term PPI users had significantly more total bacteria present in duodenal samples compared to short-term PPI users.[103] Further, a disturbance in the fecal microbiota was seen in the long-term PPI users compared to control subjects, with those in the PPI group having elevated counts of *Enterococcus* spp. (P = 0.0021), total coliforms (P = 0.0147), *E. coli* (P = 0.0227), yeasts (P = 0.0223), and molds (P = 0.0027).

These observational studies are bolstered by a prospective study performed in children who were prescribed PPI therapy for other conditions. In this study, 70 children (mean age 13.5 years), who were glucose breath-test negative at baseline, were given 20 mg of omeprazole for four weeks.[104] After the PPI treatment period, 21 of the 70 children (30%) became breath test positive and an additional five children developed symptoms of SIBO while remaining breath test negative. In this study, the use of a probiotic supplement (2 billion CFU/day of *L. rhamnosus* and *L. acidophilus*) in these children was not able to mitigate the PPI-induced SIBO (see details in probiotic section on page 14). These data strongly suggest that PPI use contributes to the increased likelihood for small intestinal microbial dysbiosis in vulnerable individuals. When possible, clinicians should help patients taper their use of PPIs, as PPI drugs rarely address the root cause of a patient's GI dysfunction (see our Road map: *Functional Strategies for the Management of Gastrointestinal Disorders* [Point Institute, 2016]).

SIBO and Pancreatic Enzyme Insufficiency

Epidemiological studies have investigated the association between SIBO and chronic pancreatitis (CP) or pancreatic enzyme insufficiency because malabsorption is common in subjects with SIBO. A systematic review and meta-analysis of nine studies found a prevalence of SIBO (by positive breath test) ranging from 14-92%, with a pooled prevalence of "SIBO" in CP of 36% (with considerable heterogeneity).[105] Considering only the studies employing the glucose breath test, the pooled prevalence was 21.7% for SIBO in CP, compared to a pooled prevalence of 73.3% in the three studies using the lactulose breath test. The studies evaluating non-surgical CP patients had a lower prevalence of being breath test positive for SIBO (N = 6, 25.7%, 95% CI: 8.1-57.6%) compared to surgical CP subjects (N = 3, 54.1%, 95% CI: 23.2-82.1%). Similarly, in another study, a breath test positive SIBO prevalence of 15% (measured via GBT) was found in non-surgical patients with chronic pancreatitis (determined by patient history, functional deficits, and/or findings on radiologic/endoscopic studies) compared to 0% in healthy controls (P = 0.029).[106] Other studies have confirmed a higher prevalence of SIBO (using breath tests) in subjects with CP, suggesting maldigestion as a cause (or common consequence) of SIBO.[107]

The Complex Relationship Between IBS and SIBO

The symptoms of SIBO (e.g., bloating, abdominal distension/pain/discomfort, diarrhea, fatigue, weakness, etc.) overlap considerably with those of irritable bowel syndrome (IBS), and many clinicians consider these conditions to be commonly associated.[43] However, epidemiological research shows that the relationship between the two conditions is not well understood, is controversial, and varies considerably depending upon the diagnostic criteria used to define SIBO (and IBS). In fact, the large variance in the frequency of SIBO in IBS subjects mirrors that found in healthy controls. Ghoshal et al. reported in their meta-analysis that the frequency of SIBO amongst those with IBS ranged from 4% to 78%, whereas it ranged from 1% to 40% in healthy controls.[108] Another systematic review and meta-analysis including 12 studies (N = 1,921 patients with IBS) reported the discrepancy in the prevalence of SIBO in IBS subjects varies by test method.[109] Namely, the average prevalence of SIBO measured via lactulose breath test was 54%, and measured via the glucose breath test averaged only 31%; as compared to a mean prevalence of just 4% for jejunal aspirate enumeration. Based on the wide discrepancy of a SIBO diagnosis in IBS subjects based on test method, the Rome Foundation does not recommend routine testing for SIBO in IBS patients.[15]

Several large systematic reviews and meta-analyses have been recently published to explore the relationship between SIBO and IBS. One (published in 2018) evaluating 50 studies, reaffirmed the heterogeneity of this relationship based primarily on how the included studies tested for SIBO (e.g., small intestinal fluid aspirate and culture [N = 5], LBT [N = 24], GBT [N = 21]), the thresholds used to define a positive test, and even which Rome criteria was used to define IBS.[110] Overall, amongst these 50 studies, the pooled prevalence of SIBO in subjects diagnosed with IBS was 38% (95% CI: 32-44), which was higher in studies diagnosing SIBO using either breath tests (40%, 95% CI: 33-46) versus small intestinal aspirate and culture (19%, 95% CI: 8-30). Among subjects with IBS, female gender (OR: 1.6, 95% CI: 1.1-2.3), IBS-D subtype (OR: 1.7, 95% CI: 1.3-2.3), and older age (OR: standard mean difference: 3.1 years, 95% CI: 0.9-5.4) were associated with increased odds of SIBO, though PPI use did not increase the odds of SIBO in those with IBS (OR: 1.1, 95% CI: 0.7-1.7). When the threshold for small intestinal fluid aspirate and culture was set at $>10^5$ CFU/mL, the prevalence of SIBO in IBS subjects was 13%, compared to a prevalence of 28% when the threshold was set at $>10^3$ CFU/mL (P = 0.02).

Since these studies spanned many years there were several different diagnostic criteria used for IBS, including Rome I, Rome II, Rome III, Manning's criteria, or other physician-specified diagnosis. SIBO was more prevalent in IBS subjects meeting the Rome I criteria (72%, 95% CI: 44-91) compared to Rome II (40%, 95% CI: 27-54), Rome III (35%, 95% CI: 28-43), or other criteria (30%, 95% CI: 22-38). Therefore, while there appears to be a fairly strong association between these two diagnoses, it is still difficult to determine the prevalence of SIBO in populations of subjects with IBS. Members of the Rome IV group have noted that the status of SIBO in IBS subjects is highly controversial and explain that the diagnostic test modality and the diagnostic criteria contribute to the variance in the prevalence of SIBO in IBS.[15] A more recent meta-analysis using a more stringent criteria for including trials (25 trials) showed a similar prevalence of SIBO in IBS subjects of 31% (OR = 3.7).[111,†]

† While beyond the scope of this mini-review, the recent discoveries linking a large subset of IBS-D subjects with a previous gastrointestinal infection may have implications for connecting SIBO and IBS. Subjects with "post-infectious IBS" appear to have antibodies to a bacterial toxin (cytolethal distending toxin [CDT]), suggesting a previous infection, and often antibodies to vinculin, suggesting an autoreactive immune response to this important gastrointestinal cytoskeletal protein. While the formal link between post-infectious IBS and SIBO is still lacking, changes in motility are proposed as a possible link between these two phenomena.

Prevention and Intervention Strategies for SIBO

Even though SIBO is usually a manifestation rooted in other GI dysfunctions (e.g., GI motility, gastric acid, anatomic factors, etc.), there is a virtual absence of studies investigating therapies that address these root causes of SIBO. Instead, therapies that aim to eradicate the "overgrowth" of bacteria (i.e., antibiotics) or increase healthy bacteria (i.e., probiotics) dominate the clinical research of SIBO. Here we discuss the evidence for those therapies. In addition, it is critical that clinicians take a detailed medical history in patients diagnosed or suspected of having SIBO, noting medications that may predispose to SIBO (e.g., narcotics, proton pump inhibitors, etc.), known GI anatomical dysfunction that were either acquired or the result of GI surgery, and other coincident diagnoses the patient may have. We agree with Quigley and Abu-Shanab in their priorities (Table 1), that treating the underlying cause(s) of SIBO is the ideal strategy, though there may be some instances where the conditions associated with SIBO are not readily reversible (i.e., visceral myopathies, jejunal diverticula, etc.).[112]

Table 1: Three Components of Treating SIBO from Quigley & Abu-Shanab Review.[112]

1. *Treat the underlying cause.*
   a. *This should be the primary focus; however, some of the conditions associated with SIBO such as visceral myopathies or multiple jejunal diverticula are not readily reversible.*
   b. *Medications associated with intestinal stasis, such as those known to inhibit intestinal motility, or the inhibition of gastric acid secretion should be eliminated or substituted.*
2. *Eradicate the growth.*
3. *Address any associated nutritional deficiencies.*

Dietary Restriction and Prebiotics

Since SIBO is characterized by altered fermentation of a variety of carbohydrates, it is common for many clinicians, nutritionists, and dietitians to recommend that patients restrict certain carbohydrates from their diet (e.g., fructose, lactose, SCD or FODMAPs, low fermentation diet, etc.).[113] There is much debate on this approach, mostly based on the long-term utility of such dietary restrictions; however, there are surprisingly few published studies investigating the role of dietary changes in non-IBS, SIBO outcomes.

There is emerging data on the relationship between the carbohydrate composition of the diet (i.e., simple sugars, fiber, FODMAPs, etc.) and the carbohydrate load of the diet; however, data in this area is inconsistent with some studies showing diets high in simple sugars are more associated with SIBO and others showing higher fiber diets are associated with SIBO. These differences may be due to discrepancy in the methods used to evaluate SIBO (e.g., breath testing versus aspirate sampling) or the patient populations studied (e.g., obese subjects, healthy subjects, IBS, etc.). One retrospective study investigated the association between SIBO and carbohydrate intake in obese subjects.[114] Comparing 60 obese subjects with normal lean controls, 23.3% of the obese subjects had a positive glucose breath test, while only 6.6% of lean subjects had a positive breath test. Using diet recall, obese subjects with SIBO consumed statistically higher amounts of carbohydrates and refined sugars and less total and insoluble dietary fiber (fermentable status not reported). In contrast, another study defining SIBO as measured via duodenal aspirate enumeration $>10^5$ CFU/mL found that a high fiber diet was associated with increased microbial counts suggestive of SIBO in the duodenal samples; however, despite meeting enumeration criteria for SIBO, the subjects did not present with GI symptoms suggestive of functional gastrointestinal disorders.[56] A small-scale, pilot intervention as part of this study, found that when subjects that had previously consumed a high-fiber diet were placed on a low-fiber, high simple sugar diet, the dietary change triggered FGID symptoms, reduced the diversity in their small intestinal microbiota as measured via 16S rRNA sequencing, and led to increases in small intestinal permeability.

An intervention study evaluated the direct effect of FODMAPs on SIBO outcomes as measured via hydrogen breath test.[115] The researchers randomized 37 healthy subjects to a baseline low FODMAP diet with either an added FODMAP supplement of oligofructose or a non-FODMAP supplement containing maltodextrin (7 g, twice per day). Like other studies, the low FODMAP diet was associated with a reduction in *Bifidobacteria* in stool samples of those taking maltodextrin whereas those in the group taking oligofructose had an increase in *Bifidobacteria*. However, breath hydrogen increased in the oligofructose supplementation group whereas breath H_2 decreased in the maltodextrin group. The difference in breath hydrogen between groups post-intervention was 27 ppm ($P < 0.01$). Colonic volume increased significantly from baseline in both groups with no significant difference between them. Colonic volume correlated with total breath hydrogen and methane. Another interesting finding was that subjects in either group with high methane production also tended to have high stool microbial diversity, high colonic volume, and greater abundance of methanogens. Another study, used retrospective reviews of patients' charts, and found that when subjects with IBS (Rome I criteria) and a positive lactulose breath test at baseline (N = 93) were placed on a 14 day exclusive elemental diet (hydrolyzed nutrients designed for quick digestion and limited microbial interaction), 80% of subjects no longer had a positive LBT.[116] Five of the remaining 19 subjects that did not show improvement in LBT at 14 days, improved after seven additional days of the diet. These studies suggest there is still much to learn about the influence of diet on the ecosystem of the small intestine in terms of microbial quantity, fermentation patterns, and how that relates to microbial diversity, metabolic function and, ultimately, the patients' symptoms.

Not surprisingly, and like the role of fiber discussed above, prebiotic supplementation is also controversial. However, emerging data suggest prebiotics may improve outcomes in some subjects with SIBO. In a small, uncontrolled pilot study, fructooligosaccharide (FOS) was given to subjects with SIBO (N = 20, breath-test positive at baseline) at a dose of 2.5 g/day for seven days after a seven-day course of rifaximin.[117] Six months after the initial treatment, subjects reported a 66% improvement of symptoms; suggesting that the prebiotic did not exacerbate symptoms in these subjects. In a larger study, subjects (N = 77) with a positive glucose breath test were randomized to either rifaximin (1,200 mg/day) or rifaximin and partially-hydrolyzed guar gum (5 g/day) for 10 days.[118] Eradication (breath-test negative) was achieved in 61% of the rifaximin-only group and in 87% of the rifaximin plus guar gum group ($P = 0.017$).

Interestingly, lactulose has been examined as a therapeutic prebiotic agent in a small group of studies, with promising potential. In a human study, chronic lactulose administration (20 g, twice per day) for eight days, was shown to reduce breath H_2 excretion ($P < 0.05$).[119] Additionally, a case report of a 48-year-old male patient with SIBO (10^{12} CFU/mL in duodenal aspirate) who did not respond to four weeks of oral antibiotic treatment (i.e., Augmentin Duo [amoxycillin 500 mg and clavulanic acid] 125 mg bid, and metronidazole [400 mg, tds]); found, upon supplementation with 10 g lactulose b.i.d. for four weeks decreased his bacterial counts to 10^7 CFU/mL, and within three days the patient's chronic diarrhea and abdominal pain were resolved. Additional treatment with 20 g b.i.d. lactulose for four weeks did not further reduce bacterial cell counts upon aspirate. The therapeutic benefits of lactulose were confirmed in the patients by ceasing, then reinitiating the lactulose therapy.[120] Lactulose has even been shown to lower rates of bacterial translocation and intestinal bacterial overgrowth compared to control in animal models, which was closely associated with increased intestinal transit and improved intestinal barrier function.[121]

Although these data are limited, and in some respects, contradictory, these results begin to challenge the notion that fermentable fibers that promote the growth of certain commensal bacteria (i.e., prebiotics) are mostly harmful in subjects with SIBO. In fact, removing fermentable carbohydrates (e.g., FODMAPS, elemental diet, SCD etc.) for short-term symptom relief may actually prolong the small intestinal dysbiosis seen in many subjects.[115] Clearly more research is needed to understand the role fiber types have on SIBO outcomes, and which fiber sources and dosage levels may be more suitable for supplementation (or avoidance) in subjects diagnosed with SIBO.

Dietary Supplementation of Nutrients

SIBO is characterized by nutrient deficiencies of several fat-soluble vitamins (i.e., A, D, E), vitamin B_{12}, iron, thiamin and nicotinamide.[17] Fat absorption appears to be compromised in some subjects with SIBO due to early bacterial deconjugation of bile acids leading to decreased formation of micelles for fat absorption.[19] Supplementation of ox bile extracts and digestive enzymes containing pancreatin, pancrelipase, or fungal-analog lipases are commonly recommended for SIBO patients (especially those with steatorrhea), though the efficacy of these supplements in subjects with SIBO has not been studied.

In addition, subjects with SIBO are often recommended to consume a daily multivitamin/mineral supplement to ensure adequate intake/absorption of nutrients known to be compromised in subjects with SIBO. Since multivitamins often do not contain adequate doses of vitamin B_{12} for oral consumption, especially in subjects with chronic cobalamin deficiency, clinicians should consider additional supplementation with at least 1 mg of oral cobalamin, which performs similar to intramuscular injections of vitamin B_{12}.[122]

Antimicrobials and SIBO

The most commonly recommended therapy for SIBO is the use of prescription antibiotics as a means to reduce the presumed overgrowth of bacteria.[123,124] Therefore, numerous clinical trials have been performed using a variety of different antibiotics, testing their efficacy in patients with SIBO. A recent meta-analysis of such trials shows that, overall, normalization of breath test (i.e., positive at baseline, negative after therapy) using one of several antibiotics is about 50% (placebo average 10%).[125] The most commonly used antibiotic tested was rifaximin, which when dosed at 1,200 mg/day had an average breath test normalization rate of 60.8% (six studies at this dose, including 283 subjects). Yet, despite their efficacy, the rate of relapse after antibiotic treatment for SIBO is notoriously high; often requiring subjects to take repeated courses of antibiotics.[123,126] In fact, one study reported that after successful SIBO "decontamination" in 80 subjects using 1,200 mg/day rifaximin for one week (verified via GBT), follow-up GBT found SIBO recurred in 12.6% of subjects after three months, in 27.5% of subjects after six months and in 43.7% of subjects after nine months, and in those with GBT positivity recurrence, all subjects had significantly increased GI symptoms. In this study, older age (OR: 1.09, 95% CI: 1.02-1.16), history of appendectomy (OR: 5.9, 95% CI: 1.45-24.19), and chronic PPI use (OR: 3.52, 95% CI: 1.07-11.64) were all significantly associated with recurrence of a positive glucose breath test.

Despite this rate of recurrence, some advocate for empiric treatment with antibiotics when SIBO is suspected or diagnosed via aspirate/culture or hydrogen breath test; even recommending a second round of empiric antibiotic treatment after recurrence.[123,124] However, this strategy requires some precautions, as the empiric use of antibiotics for SIBO is not standardized or sufficiently evidence-based. We should further note that these therapies are expensive, increase the risk for antibiotic resistance, and, ultimately, do not address the underlying root cause of the recurrent dysbiosis (i.e., SIBO is not caused by antibiotic deficiency).[123]

The potential therapeutic use of natural antimicrobial compounds, several of which have proven *in vitro* activity against many aerobic and anaerobic organisms, have not been systematically tested in subjects with SIBO. One retrospective analysis evaluating the use of several different commercially available mixtures of herbal antimicrobial agents showed a rate of lactulose breath test normalization similar to rifaxamin.[127] While this was not a controlled trial (data extracted from patient charts) in which patients were given one of four different antimicrobial formulas with very different herbal mixtures, it does demonstrate that within the clinical setting, herbal antimicrobials may be equivalent to standard antibiotic treatment for SIBO.

Probiotic Therapies for SIBO Outcomes†

The supplementation of probiotics is a common therapy for numerous gastrointestinal disorders involving dysbiosis (see extensive details in our Road map *Functional Strategies for the Management of Gastrointestinal Disorders* [Point Institute, 2016]). However, since SIBO is defined as an overgrowth of bacteria in the small intestine and its symptoms are nominally related to excess fermentation, some clinicians are reluctant to recommend probiotics in subjects suspected of having SIBO. Currently, the available evidence suggests that the use of probiotics appears to be safe in subjects with SIBO (i.e., does not exacerbate symptoms) and may be beneficial in many subjects. Interestingly, a retrospective chart review evaluating 250 patients undergoing duodenal culture set out to evaluate whether probiotic use was a risk factor for developing SIBO. Increasing age (OR: 1.37, 95% CI: 1.09-1.71), PPI use (OR: 5.03, 2.30-11.01), and narcotic use (OR: 5.19, 95% CI: 1.59-16.92) were associated with SIBO, while probiotic use was not (OR: 1.00, 95% CI: 0.41-2.46).[130] However, as we will outline here in detail, research in this area is notoriously heterogeneous (e.g., different strains, doses, SIBO diagnostic criteria, and endpoints) and difficult to interpret. Surprisingly, few studies have been adequately designed to help understand the therapeutic efficacy of probiotics for SIBO-related outcomes.[131]

Currently, only one meta-analysis (N = 18, published in 2017) has been performed to summarize the effect of probiotic supplementation for SIBO outcomes.[132] The authors defined "SIBO decontamination" broadly as measured by either: (1) reduced bacterial density, (2) hydrogen breath test normalization, or (3) improvement in the abdominal pain symptoms or bowel habits. In this analysis, the observed SIBO "decontamination" rate in nine studies following probiotic supplementation was 62.8% (51.5% to 72.8%) compared to the non-probiotic groups (RR: 1.61; 95% CI: 1.19-2.17, P < 0.02). When evaluating studies using probiotics alone, the SIBO decontamination rate was 53.2% (95% CI: 40.1% to 65.9%), whereas for probiotics plus antibiotics the decontamination rate was 85.8% (95% CI: 69.9% to 94.0%). Although these results are interesting, their clinical application is limited by the large heterogeneity between the trials in terms of the dose/strain/combination of probiotics used, the types and number of patients studied, the duration of supplementation, the techniques used to measure SIBO (e.g., aspirate and culture, hydrogen breath tests, symptom questionnaire, etc.), the defined cut off values used to describe a SIBO positive subject, the quality of the study designs (e.g., open-label, randomized, double-blind, nonrandomized, etc.), and other issues. Therefore, to help the clinician further understand the evidence related to probiotic therapies and SIBO outcomes, we include the details of several different studies below.

Probiotics Efficacy Compared to (or Added to) Antibiotic Therapy

Since the use of antibiotic therapy is quite common in subjects with SIBO and it is a common practice within the functional and integrative community to augment antibiotic therapy with probiotic supplementation, we first evaluate studies that combine (or compare) these therapies in the same study before looking at those using probiotics as a monotherapy.

An open, pilot, clinical trial evaluated the comparative and additive effect of metronidazole *or S. boulardii* for SIBO outcomes as measured via the lactulose breath test in subjects with systemic sclerosis and SIBO (N = 40).[133] SIBO patients were randomized to one of three groups as follows: (1) metronidazole monotherapy, 500 mg b.i.d orally for seven days; (2) *S. boulardii* monotherapy, 200 mg b.i.d orally for seven days; or (3) combination therapy with metronidazole and *S. boulardii*, 500 mg metronidazole + 200 mg *S. boulardii* b.i.d for seven days and then seven more days with *S. boulardii*. Results showed that the monotherapy with *S. boulardii* was more effective than the metronidazole monotherapy to improve the LBT, but the best results were obtained when *S. boulardii* was combined with metronidazole. After two months of treatment, LBT improved in 55% of the *S. boulardii* combined with metronidazole group, in 33% of the *S. boulardii* monotherapy group and in 25% of the group receiving metronidazole alone. Additionally, the groups receiving *S. boulardii* had improvements in GI symptoms (i.e., decreased diarrhea, abdominal pain, and gas/bloating/flatulence), while the metronidazole group remained unchanged in these symptoms (actually, an increase in abdominal pain and gas/bloating scores were reported with metronidazole).

Another study compared antibiotic treatment with probiotic supplementation in 50 subjects who had a positive LBT and chronic abdominal distension (Rome III).[134] Subjects randomized to the antibiotic group were given metronidazole (N = 25; Flagyl, 500 mg b.i.d.) for five days, while those in the probiotic group received a mixed strain probiotic formulation containing: *Lactobacillus casei* (3.3 x 10^7 CFU), *Lactobacillus*

† We acknowledge that taxonomic and nomenclature changes to the former *Lactobacillus* genus have been detailed in April of 2020. This genus is being split due to newer advances in technology suggesting that the genus was too diverse functionally and did not conform to nomenclature conventions. The new nomenclature changes group the former *Lactobacillus* genera into groups that share physiological and metabolic properties. Although we acknowledge this change is taking place, we use the previous nomenclature convention (i.e., *Lactobacillus*) for referring to this genus in our review as the primary source studies we review use this nomenclature. Changes are also being proposed for the genus *Bifidobacteria*, but action has not yet been made. For additional information the interested reader is directed to the following resources.[128,129]

plantarum (3.3 x 10^7 CFU), *Streptococcus faecalis* (3.3 x 10^7 CFU), *Bifidobacterium brevis* (1.0 x 10^6 CFU), b.i.d., for five days. Subjects were also asked to reduce their consumption of alcohol, legumes, dairy products, and leafy vegetables; and subjects were followed for changes in clinical symptoms (rather than objective measures of SIBO). Following treatment, greater clinical improvements were reported in subjects consuming probiotics compared to metronidazole using a clinical symptom questionnaire (82% in probiotics group vs. 52% in antibiotics group, P = 0.036). A similar study, published as an abstract, found that 2 x 10^9 spores of *Bacillus clausii* administered three times per day in subjects (N = 60) with IBS and a positive glucose breath test normalized the GBT in 56.6% of subjects (17/30 subjects) compared to a group of subjects receiving 750 mg/day metronidazole for one week, where the GBT was improved in 40% of subjects (12/30 subjects, P < 0.001).[135] Further, the incidence of GI side effects (i.e., nausea, diarrhea) was lower in the probiotic group compared to the group receiving antibiotics (P < 0.05). Though metronidazole is not the most commonly recommended antibiotic for SIBO, these data suggest a comparative benefit with some probiotic therapies.

In another study, breath testing was used as the inclusion criterion (positive defined as agreement between GBT and LBT), though like the first study above, symptom improvement (using Rome II criteria and Bristol stool scale), rather than follow-up breath testing was used as the outcome measure.[117] This study found that subjects (N = 40) with chronic abdominal symptoms (without other GI disorders or alarm symptoms) had statistically similar symptom improvement when adding either a probiotic agent (83.3% improved; *L. casei* DG at 24 "milliards of alive bacteria") or a prebiotic agent (66% improved; FOS, at the dose of 2.5 g/day) to rifaximin therapy (400 mg/day for 7 days/month) followed by the probiotic or prebiotic for seven successive days for six months. Since there was no rifaximin-only group, it is difficult to weigh the contribution of each component of the combined therapies, though these symptom improvements are similar or greater than the SIBO-normalization rate of rifaximin-alone in previously described studies.

A small pilot study in 30 subjects with chronic abdominal pain or diarrhea with a positive breath test at baseline evaluated the effects of adding a synbiotic (*Bacillus coagulans* spores and FOS- twice/day after meals, dose not specified) to maintenance antibiotic therapy (15 days of minocycline, 100 mg twice a day, during first half of each month) for six months, compared to maintenance antibiotics alone. Prior to beginning the trial, all subjects were treated at baseline with a three-week aggressive broad-spectrum antibiotic (dose and type not described). The added synbiotic therapy resulted in a higher breath test normalization rate (93.3%) compared to those on maintenance antibiotic alone (66.7%), though this difference was not statistically significant (P = 0.169).[136] The synbiotic group did, however, have significant decreases in abdominal pain and other GI symptoms (i.e., flatulence, belching, diarrhea), compared to the antibiotic-only control group. Another small-scale crossover trial (N = 10) evaluating short-term (7 days) therapy with *S. boulardii* (1,500 mg/day) did not show benefit in subjects with SIBO-related outcomes, while benefits were realized with either amoxicillin-clavulanic acid (1,500 mg/day) or norfloxacin (800 mg/day).[137] The authors note that the seven-day *S. boulardii* treatment course was likely inadequate to realize any potential benefit of the probiotic treatment.

These data are simply too limited and heterogeneous to make specific conclusions or recommendations regarding the addition of probiotics to antibiotic therapy for SIBO eradication or symptom relief. However, since there is good evidence that probiotic therapy may reduce the risk of antibiotic-associated diarrhea and/or *C. difficile*-associated diarrhea, probiotic use may benefit the patient regardless. The question of whether probiotics (instead of antibiotics) may be an effective strategy has been investigated in several clinical studies, to which we will now turn.

Probiotics Tested as Stand-Alone Therapy

As is the case for studies investigating probiotics with, or in comparison to, antibiotics, studies which evaluate probiotics as a monotherapy in placebo-controlled or uncontrolled trials are also limited and quite heterogenous. In many cases, probiotic therapies for SIBO-related outcomes are performed in quite vulnerable subjects (e.g., gastric or colorectal cancer) or with other functional bowel disorders (e.g., IBS, etc.).

For example, an open-label study evaluating probiotics as a standalone therapy for SIBO in IBS subjects (defined by Rome II) was performed.[138] In this study, IBS subjects were deemed to have SIBO based upon aspirate and culture of the third part of the duodenum using a threshold value of >10^5 CFU/mL of bacteria and/or the presence of colonic type bacteria in the aspirate sample. The authors aimed to enroll 30 IBS subjects with SIBO and 30 without SIBO; however, only five IBS subjects with SIBO and 21 subjects without SIBO were enrolled in the trial. Both groups received a mixed-strain probiotic supplement (*S. boulardii* [1.5 x 10^9 CFU], *B. lactis* BB-12 [1.75 x 10^9 CFU], *L. acidophilus* LA-5 [1.5 x 10^9 CFU], *L. plantarum* [0.5 x 10^9 CFU]) every 12 hours for 30 days. Following probiotic treatment, total IBS score was reduced by 71.3% in IBS subjects with SIBO compared to only 10.6% in those without SIBO (P = 0.017). In fact, a >50% decrease in total IBS-Severity Scoring System (SSS) was realized by all IBS subjects with SIBO by the third follow-up visit, compared to only 38.1% of subjects without SIBO (P = 0.039). While these data are promising, the lack of full enrollment and use of symptom scores alone (rather than follow-up aspirate and enumeration or breath test) limit the interpretation of this trial.

One of the earlier studies conducted to test the effects of probiotics on breath hydrogen (baseline) was a small-scale study that included 22 subjects with elevated breath hydrogen and chronic diarrhea. These subjects were randomized to either a probiotic supplementation (3.0 g lyophilized *L. casei* and *L. acidophilus* strains CERELA, CFUs unspecified) or placebo (3 g maize starch) twice daily for 21 days.[139] Following treatment,

those in the probiotic group saw a reduction in breath hydrogen compared to control at seven ($P < 0.005$), 15 ($P < 0.001$) and 21 days ($P < 0.0001$); however, this effect was not sustained after withdrawing probiotics after 15 and 21 days, suggesting continuous probiotic supplementation may be needed to sustain the benefit. Additionally, a significant reduction in mean daily stools was observed with probiotic supplementation compared to placebo ($P < 0.005$) at 15 days and 21 days ($P < 0.0005$). In another preliminary, open-label, uncontrolled study, 14 subjects with IBS (Rome II criteria) with a positive lactulose breath test (early rise) were supplemented with a probiotic drink containing *L. casei* strain Shirota (6.5×10^9 CFU, taken each morning before breakfast) for six weeks.[140] Following treatment, the median time to increase breath hydrogen ≥10 ppm H_2 was increased in probiotic group compared to baseline (75 min vs. 45 min, $P = 0.03$); and 64% no longer had an early rise in H_2 ($N = 9$) following treatment (i.e., became breath test negative).

Another study ($N = 50$) found supplementation with combined live *Bacillus subtilis* and *Enterococcus faecium* (500 mg, three times per day, CFU concentration not disclosed) for four weeks was associated with a reduction in the percentage of subjects with a positive LBT for SIBO (60% at baseline versus 28% after supplementation) in subjects with symptoms of functional bowel disorders who had previously undergone bowel preparation with polyethylene glycol electrolyte powder and colonoscopy.[141] In contrast, the control group saw a slight increase in the percentage of patients with a positive LBT indicative of SIBO after four weeks (52% at baseline versus 56% after four weeks, $P = 0.254$). Those in the probiotics group also saw a change in their fecal microbiota and a significant reduction in gastrointestinal symptoms compared to placebo after four weeks of supplementation ($P < 0.001$). Another open-label study evaluating subjects ($N = 40$) with GI symptoms (e.g., bloating, flatulence, abdominal discomfort/pain, diarrhea) and an abnormal glucose breath test investigated the effects of the spore-forming organism *Bacillus clausii*.[142] In this open-label study, subjects received 2×10^9 spores of *Bacillus clausii* three times per day, for one month. Following probiotic treatment, glucose breath test normalized in 47% of subjects (19/40), and the treatment appeared to be safe and well tolerated. These preliminary results, though promising, have yet to be confirmed in a controlled clinical trial.

An open-label, single-blind, small clinical trial evaluated the effect of supplementation with a multispecies probiotic formula in male IBS-D patients (Rome III criteria, $N = 10$) with the primary aim to assess the degree of abdominal symptom relief and changes in the fecal microbiota.[143] The probiotic formula consisted 25 billion active bacteria with 12 different strains: *L. rhamnosus* 6.0 billion CFU, *B. bifidum* 5.0 billion CFU, *L. acidophilus* 3.0 billion CFU, *L. casei* 2.5 billion CFU, *L. plantarum* 2.0 billion CFU, *L. salivarius* 2.0 billion CFU, *B. longum* 1.0 billion CFU, *S. thermophilus* 1.0 billion CFU, *L. bulgaricus* 1.0 billion CFU, *L. paracasei* 0.5 billion CFU, *B. lactis* 0.5 billion CFU, and *B. breve* 0.5 billion CFU. At baseline, six of the ten subjects with IBS-D had an abnormal LBT indicative of SIBO, and after eight weeks of supplementation with probiotics, LBT improved into the normal range in two of the six subjects. Although the small intestinal microbiota was not profiled, probiotic treatment after eight weeks was shown to reduce the operational taxonomic units significantly in stool samples ($P = 0.018$). Further, molecular analysis of the fecal microbiota showed a favorable shift in the microbial composition. Abdominal discomfort, dyspepsia, flatulence all significantly improved after probiotic supplementation; however, epigastric pain was not significantly improved. This trial is important to highlight as it suggests that probiotics given to subjects with an abnormal LBT improved subjective symptoms, was associated with improved fecal microbiota profile, and even improved SIBO status in several subjects.

A randomized, double-blind crossover trial was conducted using 14 patients with longstanding SIBO (as defined by patients fulfilling at least two of three criteria indicative of SIBO: duodenal aspirate and culture, hydrogen breath testing with 50 g glucose as substrate, or via clinical response to antibiotic treatment). After four weeks of treatment with *L. fermentum* KLD given at a dose of 10^{10} CFU twice daily, there was no significant difference compared to placebo for glucose hydrogen breath test, stool frequency, or symptom score – although across all subjects, the placebo group was associated with non-statistically lower values for GBT, stool frequency, and symptom scores.[144] However, in four of five subjects with the most elevated breath hydrogen values at baseline, treatment with *L. fermentum* KLD reduced their glucose breath hydrogen response after four weeks of probiotic supplementation, although the significance could not be assessed due to the low numbers of subjects.

Three additional studies have been published exploring the effect of probiotic supplementation as a standalone therapy on hydrogen breath test outcomes in very specific and vulnerable patient populations. First, subjects ($N = 53$) with chronic liver disease (i.e., alcoholic liver disease, chronic hepatitis B, chronic hepatitis C) were randomized to supplementation with either a multi-strain probiotic therapy containing six strains: *B. bifidum* (KCTC 12199BP), *B. lactis* (KCTC 11904BP), *B. longum* (KCTC 12200BP), *L. acidophilus* (KCTC 11906BP), *L. rhamnosus* (KCTC 12202BP), and *S. thermophilus* (KCTC 11870BP), containing 5×10^9 CFU/capsule or placebo.[145] Subjects took the probiotic or placebo twice daily for four weeks. At baseline, SIBO (measured via lactulose breath test) was diagnosed in 26% of the chronic liver disease study population. Following four weeks of supplementation, the lactulose breath test was normalized in 24% of those in the probiotic group compared to 0% in the placebo group ($P < 0.05$). In addition to the lactulose breath test improvements, those in the probiotic group reported more improvements in GI symptoms than did the placebo group. Despite these positive changes, liver chemistry and Child-Pugh scores did not improve significantly in either the probiotic or placebo groups.

Probiotics were also shown to benefit subjects with cirrhosis without overt hepatic encephalopathy in a study randomizing subjects (N = 160) to treatment with a probiotic containing: *B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. bulgaricus* and *S. thermophilus* (VSL #3) containing 1 x 10^8 CFU, three times daily or placebo.[146] After three months of probiotic treatment, breath-test positive SIBO (via GBT) was shown to significantly decrease (33 subjects at baseline vs. 14 subjects after three months supplementation, P = 0.006). The placebo group had no significant change in SIBO status (26 subjects at baseline vs. 21 subjects after three months of supplementation, P = 0.91). Orocecal transit time measured via lactulose breath test was significantly reduced (i.e., transit was quicker) after probiotics therapy (compared to baseline 138.6 vs. 112.3 minutes, P = 0.05); whereas the placebo group showed no significant change in orocecal transit time (145.6 vs. 141.7 minutes, P = 0.85). Significantly fewer subjects in the probiotic group (N = 7) developed overt hepatic encephalopathy compared to the placebo group (N = 14, P < 0.05), with a hazard ratio of 2.1, comparing the control group to the probiotic group (95% CI: 1.31-6.53). No adverse events were observed with probiotic supplementation in this trial.

The final study evaluating a vulnerable population was designed as a two-part study which initially studied the incidence of SIBO in patients with gastric (N = 112) and colorectal cancer (N = 88) via an observational design, and then used a randomized, double-blind study design to evaluate the effect of probiotic supplementation in these patients.[147] The authors reported that 65.2% of the gastric cancer patients had SIBO (GBT positive) and 60.2% of those with colorectal cancer tested positive for SIBO, compared to 16.3% of the healthy control subjects measured (N = 126). In subjects with cancer, SIBO was significantly associated with PPI use. For the intervention part of the study, subjects were randomized to either probiotic supplementation (N = 63, "*Bifidobacterium* triple viable capsule," dose and species/strains were not specified) or to placebo (N = 63) for four weeks. Following treatment, only 19% of subjects receiving the probiotic were breath test positive for SIBO, while 74.6% of subjects in the placebo group were breath test positive (P < 0.01). Additionally, probiotic treatment was associated with significant improvement in GI-related symptoms compared to placebo (P < 0.05).

Probiotics and Methane Production

Limited studies have evaluated the effect of probiotic supplementation on breath methane levels and have found inconsistent results. The first study was retrospective and found supplementation with *L. reuteri* (DSM 17938) given at a concentration of 10^8 CFU, 30 minutes after eating, twice per day, for four weeks in adults with functional constipation (N = 20) significantly reduced the mean methane production as measured by LBT.[148] Prior to *L. reuteri* supplementation, the mean methane level in these subjects following LBT was 20.8 ppm which was significantly reduced to 8.9 ppm following four weeks of probiotic supplementation (P < 0.0001). Further, a reduction of methane <5 ppm was seen in eleven patients, equating to 55% of the patient population studied. However, no significant decrease in hydrogen gas was found (from 13.2 to 11.4 ppm, not significant). Patients also experienced a significant increase in the number of bowel movements per week at the end of probiotic supplementation (from 4.1 to 6.4, P < 0.001). Despite these results, another small human study, evaluating a different probiotic strain (*B. infantis* 35624) in a different patient population (healthy subjects) found the opposite effect on breath methane levels. In this study, *B. infantis* 35624 (given in an undisclosed dose) for two weeks did not affect breath hydrogen measured via LBT (P = 0.768) but did lead to significantly higher levels of methane in the breath when comparing the baseline LBT to the post-probiotic supplementation LBT (P = 0.012).[149] Although these results are interesting, this is a small study that may be limited by the lack of standardization of the diet during the probiotic supplementation phase. Further, there was no control group for comparison over time and there was also a high rate of positive LBT in the asymptomatic healthy population at baseline. These small studies highlight the need for additional research specific to the effect of probiotic supplementation on breath methane levels.

Probiotics for SIBO Prevention in Subjects using PPIs

As discussed previously, epidemiological evidence suggests there is an association between PPI use and SIBO incidence. Therefore, several studies have been designed to investigate the potential for probiotic therapies to reduce the incidence of SIBO in subjects consuming PPIs. Earlier we described a trial performed in children given probiotics supplementation concurrent with initiating PPI therapy. In this study, 70 children with complaints of epigastric pain were treated with 20 mg omeprazole per day for four weeks and were either randomized to additional supplementation with a probiotic (N = 36) or a placebo (N = 34).[104] The probiotic consisted of *L. rhamnosus* R0011 (1.9 x 10^9 CFU) and *L. acidophilus* R0052 (1 x 10^8 CFU), one capsule was given per day. After four weeks of treatment, there was no difference in the incidence of PPI-induced positive GBT in subjects taking the probiotic or placebo (33% vs. 26.5%, P = 0.13); therefore, the authors concluded these probiotics taken for four weeks concurrently with PPI did not decrease the risk to develop SIBO.

However, in a 2018 randomized trial, 128 children (1-18 years old) with gastroesophageal reflux disease (GERD) were treated with a PPI drug, esomeprazole (1 mg/kg/day, 40 mg maximum dose) and were concurrently randomized to either probiotic supplementation with *L. reuteri* DSM 17938 (oil suspension, 1 x 10^8 CFU/day) or placebo for 12 weeks to study the incidence of SIBO measured via glucose breath test.[150] At baseline (prior to treatment with PPI) both the probiotic and placebo groups had a normal glucose breath test, indicating that subjects were breath test negative for SIBO at baseline, which was compared to a group of healthy children controls (N = 120) having a breath-test positive SIBO prevalence of just 5%. However, after

12 weeks of supplementation with the PPI, a 56.2% incidence of breath-test positive SIBO was found in the placebo group, which was significantly greater than the 6.2% incidence found in the PPI and probiotics group ($P < 0.001$). In contrast to the previous study, this trial suggests probiotic therapy with *L. reuteri* DSM 17938 was able to attenuate or prevent the increase in H_2 using the GBT following PPI use. While it is tempting to attribute this difference to a species-specific effect, since *L. reuteri* can produce reuterin (a known antimicrobial substance), more studies using other strains and species are needed to make these conclusions.[151]

Additionally, a small-scale intervention arm was added to one of the PPI-related studies discussed previously. This study compared the prevalence of SIBO in long-term PPI users (>12 months), short-term PPI users (3-12 months), and control subjects to test whether probiotic supplementation with N-acetyl-cysteine (NAC, as a biofilm disrupter) would affect SIBO status in the long-term PPI group.[103] Ten subjects taking PPI medication for longer than 12 months were given probiotic treatment for ten days (sachet containing: *L. rhamnosus* LR06 [DSM 21981], *L. pentosus* LPS01 [DSM 21980], *L. plantarum* LP01 [LMG P-21021], and *L. delbrueckii* subsp. *delbrueckii* LDD01 [DSM 22106], 10 billion CFU/sachet plus 60 mg NAC), while ten subjects with long-term PPI use given no treatment served as controls. After ten days, probiotics/NAC supplementation significantly reduced total bacteria (measured via gastroscopy) in long-term PPI users (8.60 log CFU/mL baseline [equivalent to 3.98×10^8 CFU/mL] vs 7.71 log CFU/mL after treatment [equivalent to 5.13×10^7, $P = 0.0023$]) for gastric juice samples, and a significant reduction in total bacteria in the duodenal brushing samples comparing baseline (8.32 log CFU/mL equivalent to 2.09×10^8 CFU/mL) to after probiotic/NAC treatment (7.47 log CFU/mL equivalent to 2.95×10^7 CFU/mL, $P = 0.0256$). Further, a significant decrease in fecal *Enterococci* spp. ($P = 0.0155$), total coliforms ($P = 0.0064$), *E. coli* ($P = 0.0105$), molds ($P = 0.0053$), and yeasts ($P = 0.0066$) was observed after long-term PPI users supplemented with probiotics/NAC for ten days. In this study, probiotics and NAC were very well tolerated.

The Therapeutic Potential of Probiotics

The research investigating the benefits of probiotic supplementation in SIBO (or breath test positive) subjects appears promising, though many of these studies are preliminary in nature and have many methodological limitations. In fact, several studies were too preliminary to be summarized here.[152,153,154,155] Therefore, it is difficult to make reliable recommendations for specific probiotic strains and doses indicated for SIBO patients. Nonetheless, we make these important observations about the current research status for clinicians to consider:

- Probiotics (of diverse species) used in published clinical trials ***do not*** appear to exacerbate SIBO symptoms when compared to placebo in a wide range of subjects; though we acknowledge that there are many anecdotal descriptions of, or speculations about, adverse outcomes.[156,157]
- Some, though not all, trials suggest that probiotic therapy reduces GI-related symptoms or breath test results in subjects diagnosed with SIBO.
- Currently there are insufficient studies using the same species (or strain) of probiotic, or head-to-head studies, to suggest a species-specific benefit for any available probiotic strain or strain combination regarding SIBO outcomes.
- From the currently available evidence, it does not appear that probiotic therapy harms the efficacy of antibiotics and (based on limited studies) may have the potential to improve the eradication rate when added to antibiotic therapy.

Summary

In many ways, it is difficult to argue with Khoshini et al. when they note that "*the single most significant problem in defining SIBO is that it is not a disease. SIBO is an epiphenomenon of some other bowel disorder. Therefore, there is no gold standard patient let alone gold standard test. Each patient with gastrointestinal disease may have different abnormal levels of small bowel bacteria.*" [13] As we have shown, the research related to SIBO bears this out, in that the definition, symptoms, causes, diagnostic tests, and test cutoff criteria lack uniformity across the many groups studying this phenomenon. Whether new diagnostic technologies will clear up this confusion is yet to be seen.

We believe that the "overgrowth" emphasis of SIBO (which often is not substantiated by the literature) often leads to an overuse of antibiotic therapies in these subjects. This is especially true given the recurrence rates of SIBO after antibiotic therapies that are noted in the literature. In general, we believe dysbiosis of the small intestine is most often a result of one of several underlying anatomic and physiologic abnormalities within the gastrointestinal tract (e.g., failure of gastric acid barrier, dysmotility, etc.), and remind clinicians to consider evaluating and treating these root causes of the "SIBO" presentation as they consider the best means of eradication (if necessary). As with many complex functional conditions, therapies that work for one patient will not always work for another; and therapies designed for temporary symptom relief (i.e., avoiding FODMAPs), may not be helpful as a long-term preventative strategy. However, with patience, the careful clinician should have the available tools to greatly improve the health of even the most challenging patient suffering with SIBO.

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This Monograph expands on the work found in our Road Map, *Functional Strategies for the Management of Gastrointestinal Disorders: Principles and Protocols for Healthcare Professionals* (Point Institute, 2016). This book includes a wide range of topics focused on supporting the key functions of the GI tract: digestion, absorption, elimination, barrier function, neuroendocrine and the microbial ecosystem.

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